Liver Cell Adenomas

A 12-Year Surgical Experience From a Specialist Hepato-Biliary Unit

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Twenty-four patients with liver cell adenomas were referred to Paul Brousse Hospital between 1976 and 1987. This represents the largest reported surgical experience of this pathology from a single centre. Six patients had multiple adenomas, which were associated with glycogen storage disease in four. Two patients had polyadenomatosis, one of whom underwent successful liver transplantation after malignant transformation to hepatocellular carcinoma. Eighteen patients (median age of 33 years, range of 17–45 years) had either a solitary adenoma or two adenomas. Eighty-three per cent were women 87% of whom had received oral contraceptives or other hormone therapy before diagnosis (median duration of 11 years, range of 3–15 years). Fifty per cent of these patients presented with acute hemorrhage into an adenoma. Seventeen patients underwent surgical resection of their adenomas, with the remaining patient currently being treated by arterial embolizations to reduce the tumor size before surgery. There was no operative mortality or serious morbidity, and all patients remain well upon follow-up. Surgical excision of liver adenomas, where this can be done without causing mortality, is recommended. Resection relieves symptoms and removes both the risks of hemorrhaging into the tumour and of malignant transformation to hepatocellular carcinoma.

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LIVER CELL ADENOMAS are rare benign tumors, the incidence of which has increased since the introduction of oral contraceptives.[1] These tumors are seen principally in women during the period of their reproductive activity. Most of these women exhibit symptoms, but asymptomatic adenomas are detected with increasing frequency after imaging of the liver for unrelated pathology.

The treatment of these lesions remains controversial for four primary reasons. First, there has been a certain amount of confusion involved in the classification of benign liver tumors, and in particular over the distinction between adenoma and focal nodular hyperplasia.[2,3] Their respective risks are better understood today.[4] Second, the frequency of hemorrhagic complications of adenomas is difficult to estimate because there are few large series of these patients from one institution. Third, the risk of transformation to hepatocellular carcinoma is still unclear.[1] And fourth, the technical difficulties encountered in the excision of these tumors has lead to too wide a variety of excision policies. Some authors believe that the decision regarding excision should be based on the operative risk[4–8] or size[3,9] of the adenoma or on the presence or absence of symptoms,[3,10] whereas others are relatively conservative,[7,9,11–13] prefering to observe the tumors after the patient is withdrawn from hormone therapy or proposing alternative treatments such as embolization of the arterial supply to the tumor.[5]

The aim of this study is to report the experience of a specialist hepatobiliary unit that specializes in the treatment of liver adenomas. We will explore the parameters determining the therapeutic decisions and describe the surgical resections performed, in an attempt to define a logical approach to the indications and techniques of surgical resection of these tumors.

Patients

Between 1976 and 1987, a definite diagnosis of liver adenoma was made in 24 patients, aged 4–45 years, referred to the Paul Brousse hospital group in Paris. The diagnosis was made by experienced hepatobiliary pathologists based on either the histology of the resected specimens (21 patients) or on biopsies performed at laparotomy (three patients), corresponding to the pathological criteria previously described.[14] Particular care was taken to differentiate between these lesions and focal nodular hyperplasia or well-differentiated hepatocellular carcinoma.

The clinical notes and morphologic investigations of these patients were reviewed. The adenomas were con-

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TABLE 1. *Patient Details*

Patient Number	Age (years)	Sex	Tumor Diameter (cm)	Topography within the Liver (Segments)	Surgical Procedure	Blood Transfusion (units)	Postoperative Hospital Stay (days)
Multiple adenomas							
1	4	M			Tumorectomy	0	5
2	5	M			Biopsy	0	7
3	14	M			Biopsy	0	4
4	21	M			Hepatic transplantation	8	24
5	45	F			Tumorectomy	0	11
6	18	M			Hepatic transplantation	5	26
Solitary or two adenomas							
7	27	M	14	VII, VIII, I	Right hepatectomy	5	12
8	44	M	13	IV, V	Tumorectomy	3	13
9	17	M	2	IV	Tumorectomy	0	12
10	38	F	13	IV, V, VIII	Tumorectomy	1	14
11	38	F	20	II, III	Left lobectomy	6	12
12	26	F	5	III	Tumorectomy	0	9
13	33	F	17	VIII	Tumorectomy	8	11
			5	IV	Segmentectomy		
14	25	F	15	V, VI	Tumorectomy	0	14
15	43	F	10	II, III, IV	Left lobectomy + Tumorectomy IV	0	10
16	45	F	18	IV, V, VI, VII, VIII	Right hepatectomy	4	12
17	39	F	12	V, VI, VII, VIII, I	Right hepatectomy	3	11
18	37	F	8	VII, VIII	Right hepatectomy	7	12
19	28	F	18	IV, V, VI	Trisegmentectomy	4	11
20	27	F	20	IV, V, VI, VII, VIII	Biopsy	0	6
21	29	F	8	VI	Tumorectomy	0	8
			5	IV	Tumorectomy		
22	42	F	15	II, III	Left lobectomy	0	6
23	33	F	8	VII	Tumorectomy	0	9
24	23	F	18	VII, I	Right hepatectomy	3	18

sidered responsible for the patients' symptoms when no other pathology explaining them was discovered. The topography of the tumors within the liver was described, using the anatomic classification of Couinaud.[15] The precise vascular relationships of the tumors were defined in 20 patients who underwent coelio-mesenteric angiography and pre- and/or peroperative ultrasonography of the liver.[16] Tumor size was measured at ultrasonographic examination. The term "adenomatosis" was reserved for patients with multiple (greater than ten) adenomas in an otherwise normal hepatic parenchyma and without a history of androgenic steroid therapy or glycogen storage disease.[17]

Operative Techniques

All resections were undertaken as elective operations. Tumorectomies were performed as excisions passing within 2 cm less of the limits of the tumor. Anatomical resections were performed as previously described.[18] The ultrasonic dissector (Cavitron, Laser Sonic Voltaire, 0210 Aisne, France) was used from 1985 on, particularly when the adenoma came into contact with one of the three principle hepatic veins. Before 1985, liver resection was performed using the digits or Kelly arterial forceps to fracture the liver substance, thus exposing the hepatic portal pedicles and venous radicles for individual ligation. Vascular exclusion of the liver, using standard techniques, was performed when a central tumor displaced the portal bifurcation or hepatic veins. Blood transfusion was performed so as to maintain hemodynamic stability and a normal hemoglobin and hematocrit both during and after surgery.

Results

Of the 24 patients studied, six had multiple adenomas and eighteen had either a solitary adenoma or two adenomas only (Table 1).

Multiple Adenomas

Patients 1–4 suffered from glycogen storage disease (Type I in the case of three patients and Type III in the case of one). In two of these patients (4 and 5 years old, respectively), the adenomas were discovered at laparotomy before portocaval anastomosis. The diagnosis was confirmed by needle biopsy in one, and by excision biopsy of a 1-cm lesion in the other. A third child (14 years old)

underwent laparotomy and biopsy of multiple lesions initially discovered on hepatic angiography. The fourth patient (21 years old) has undergone orthotopic liver transplantation for chronic cholestasis due to compression of intrahepatic bile ducts by large adenomas. The remaining patients (Patients 5 and 6) suffered from adenomatosis. Patient 5, a woman 45 years of age, had taken oral contraceptives for only 15 days 20 years before referral to our institution. She presented with sudden onset of upper abdominal pain, associated with hemorrhage into a 5-cm adenoma in segment five. This lesion was resected, at which time multiple (>50) adenomas were noted throughout the liver. Except for two further episodes of acute pain, again related to hemorrhage into adenomas, she has remained well during the 6 years of follow-up. These episodes settled with conservative treatment. Serum alphafetoprotein concentrations have remained within normal range.

Patient 6, aged 16 years, was referred to us only after his adenomatosis had degenerated. He had never received hormonal therapy and was not diabetic. At the age of thirteen, after suffering mild trauma, he had undergone emergency laparotomy for abdominal pain at another hospital. The laparotomy revealed hemoperitoneum from a ruptured nodule in the left lobe of the liver. Multiple nodules were present throughout the liver. Left lobectomy was performed and histology revealed adenomas. The tumor-free liver was normal. Ultrasonography and computed tomography (CT) confirmed numerous (>50) hyperechogenic hypodense nodules throughout the remaining liver that remained stable over a period of 3 years. At this time, he was the subject of a published study.[17] On further follow-up, 5 years after the original resection, although there was no gross change in the morphology of the hepatic lesions, the alphafetoprotein concentration, which had previously been normal (<9 IU/l), rose dramatically to 300,000 IU/l over a period of 6 months. Malignant transformation was suspected and he underwent uneventful orthotopic liver transplantation in February 1987. He remains well. The resected liver weighed 3.6 kg and contained multiple areas of well-differentiated hepatocellular carcinoma, among which were areas histologically recognizable as adenoma. The nontumoral liver was normal.

Single or Two Adenomas

Of 18 patients, 16 had a solitary adenoma and two had two adenomas (Table 1). There were 15 women (median age of 33, range of 23–45 years) and three men (17, 27, and 44 years of age). Eleven of the 15 women had taken combined estrogen/progestogen oral contraceptives (median of 11 years, range of 5–15 years), and two had taken other hormone preparations (danazol and clomiphene citrate) for a period of 3 years before diagnosis. The remaining two women and three men had no history of hormonal therapy. No patients were diabetic.

Nine patients (50%) without a history of trauma presented with sudden upper abdominal pain after hemorrhage into an adenoma. This was followed by pyrexia, often associated with elevated white cell count and mild anemia, and occasionally associated with mild biochemical anicteric cholestasis. The acute pain subsided over a period of 1–5 days, and was usually replaced by a mild chronic discomfort. All of these nine patients had previously been asymptomatic. One patient underwent emergency laparotomy and evacuation of hematoma. The tumor was not resected because its limits were not easy to define, due to the disruption produced by the hemorrhage. Three months later, subsequent morphologic examinations revealed a well-defined residual adenoma, which was resected electively. Other presentations included chronic pain of the upper right quadrant (two patients), a painless abdominal mass (two patients), and hematuria (two patients), or hypertension (one patient) due to compression of the right kidney by the hepatic tumor. The adenomas of the remaining, asymptomatic patients were discovered during investigation of a raised gamma glutamyl transferase (one patient) and raised inflammatory markers (one patient). Two patients were kept under observation elsewhere after discontinuing usage of oral contraceptives for 1 and 3 years before referral, respectively. In one patient, the hepatic tumor remained stable, and in the other, it increased in size.

Upon examination, the only significant finding in these patients was hepatomegaly that was occasionally tender. By the time of referral, routine blood tests, including liver function tests, were usually normal. No patient had elevated serum alphafetoprotein concentrations.

Ultrasonographic examination generally revealed hyperechogenic tumors with hypoechogenic centers when hemorrhage had occurred. On CT, the tumors appeared as focal defects on the static image that were highly vascular on contrast enhancement with an avascular center when hemorrhage had occurred. Angiography was the most valuable investigation. The adenomas appeared as hypervascular well-circumscribed tumors (Fig. 1) supplied by a number of arteries that were displaced around the surface of the tumor, causing the margins of the tumor to appear hyperemic. The vascular supply was therefore from the periphery to the center of the tumor via a leash of vessels passing into the tumor substance. There was a dense tumor blush during the venous phase. In the presence of hemorrhagic infarction, the center of the tumor appeared avascular (Fig. 2). A spoke-wheel pattern with central venous supply and vessels radiating to the periphery, late venous pooling, and tortuous vessels were usually

associated with focal nodular hyperplasia. Vascular leaking, arterovenous shunting, and portal venous invasion were associated with hepatocellular carcinoma.

It was not always possible to differentiate with certainty between adenoma, angioma, focal nodular hyperplasia, and well-differentiated hepatocellular carcinoma by morphologic investigations, and biopsies were therefore obtained. Percutaneous biopsies were avoided because of the risk of bleeding from these hypervascular lesions, the errors in sampling, or the potential seeding should the lesion have been malignant. Biopsies were obtained at laparotomy before the commencement of definitive surgery.

Macroscopically, the tumors appeared as soft, sharply circumscribed masses, usually lighter in color than the adjacent liver and often with large surface vessels. The topography and largest diameter of the tumors are given in Table 1. This diameter was <5 cm in four adenomas, 5–10 cm in another four, and >10 cm in 12. Upon resection, eleven of the 19 resected adenomas showed macroscopic areas of hemorrhage, including those adenomas of all nine patients who presented with acute abdominal pain.

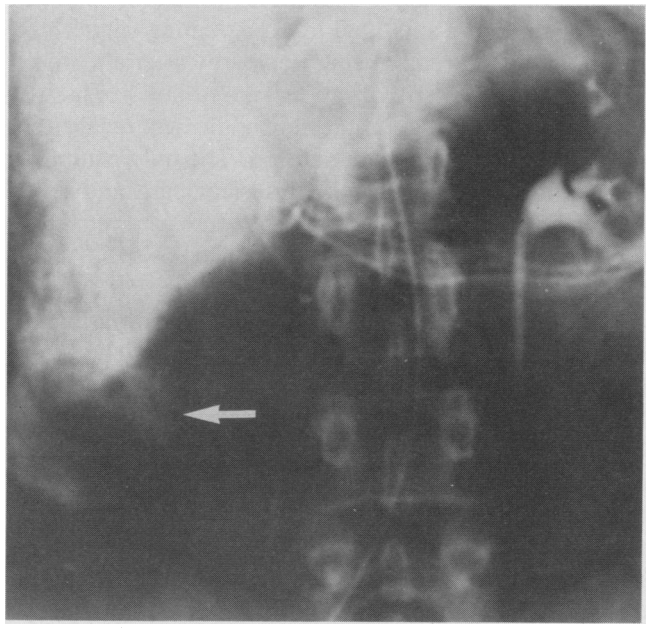

FIG. 2. Hepatic arteriogram revealing a well-circumscribed hypervascular lesion (arrow) arising from Segment VI. The center of the lesion is hypovascular, representing recent hemorrhage into the adenoma.

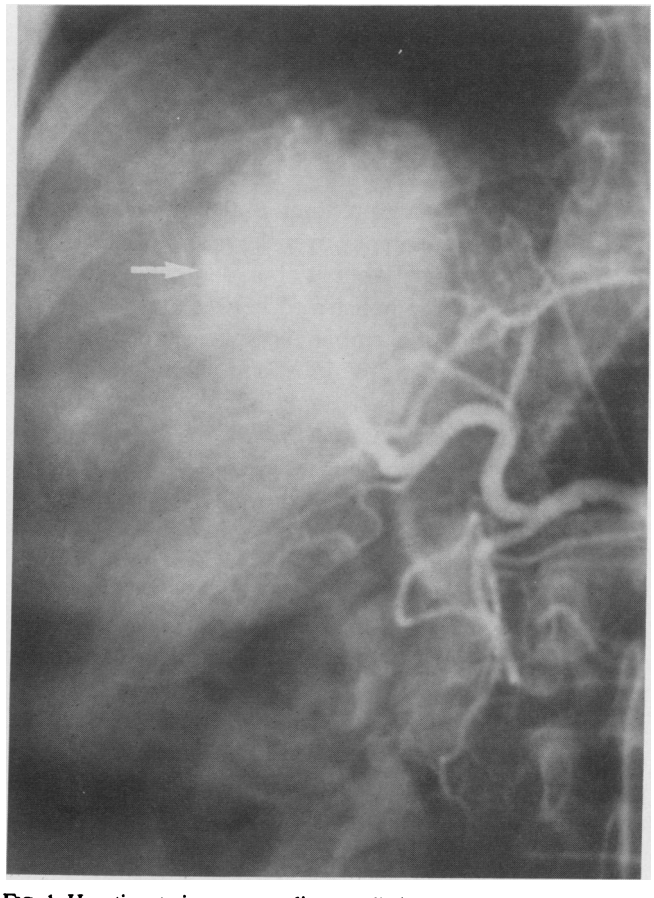

FIG. 1. Hepatic arteriogram revealing a well-circumscribed hypervascular lesion (arrow) located centrally in the liver.

Microscopically, the neoplastic cells closely resembled normal hepatocytes and showed no features suggestive of malignancy. At the periphery, the cells were often larger and paler, whereas centrally they tended to be darker, showing an irregular plate pattern. The tumors were highly vascular with multiple thin-walled sinusoids. There was a notable absence of fibrosis, portal radicles, bile duct radicles, cellular pleomorphism, and vascular invasion. Twelve of the 18 resected tumors had a definite capsule, although this was usually thin and was not visible upon ultrasonographic or CT investigations. Where hemorrhage had occurred, the capsule was disrupted.

Four patients with large vascular adenomas of the right lobe extending centrally underwent embolization of the arterial supply to the tumor with spongel to reduce the tumor size and vascularity. Three of these patients (Patients 10, 16, and 19) underwent two embolizations, separated by an interval of 3 months, before surgical resection. In all cases, the largest diameter of the tumor was reduced; in two this was by more than 50%. The fourth patient (Patient 20) presented with hypertension due to compression of the right renal artery by a 20-cm adenoma occupying the entire right side of the liver and Segment IV. Initially, the tumor was observed. Hypertension persisted and the size of this tumor had not changed 3 years after the patient's discontinuance of oral contraceptives,

at which time the patient was referred to us for treatment. The patient had a small left lobe preventing surgical excision, and is currently being treated by arterial embolizations. After four embolizations, the tumor size has decreased, thus relieving compression of the right renal artery with resolution of the hypertension. The only complications after embolization were transient pain and fever, although Patient 20 also experienced transient renal dysfunction after the major cytolysis induced by the first embolization.

A complete resection of one or both adenomas has already been achieved in 17 of the 18 patients. The extent of the surgical resections, the volume of perioperative blood loss, and duration of the postoperative stay in the hospital are given in Table 1. Eight patients underwent tumorectomy, five underwent right hepatectomy, three underwent left lobectomy, and one underwent trisegmentectomy (Segments IV, V, VI). The patient awaiting surgery will probably require right hepatectomy. Total vascular exclusion of the liver was performed in three patients (Patients 7, 8, and 10) to facilitate the resection of centrally placed tumors. Median blood transfusion was three units (range of 0–8 units). Median postoperative stay was 12 days (range of 6–18 days). There was no associated mortality and the only significant postoperative complication was one wound infection requiring drainage. On follow-up (median of 4 years, range of 6 months to 10 years) all patients are alive and well with no evidence of recurrent tumor. All have been advised to avoid hormone therapies.

Discussion

Multiple Liver Adenomas

Fifty to 80% of children with Type I or III glycogen storage disease develop multiple hepatic adenomas. These are usually diagnosed with the second decade of life, but can occur as early as at 3 years of age.[19–21] Two of the children admitted to our institution were younger than 10 years old. These tumors may hemorrhage, but they also have malignant potential, with transformation to hepatocellular carcinoma having occurred in at least four patients.[19–23] Porto-caval anastomosis improves most manifestations of the disease, but does not prevent hypoglycemia or the development of adenomas. Two of our children were referred for porto-caval anastomosis, but this treatment has since been supplanted by continuous night-feeding schedules that effectively control hypoglycemia and may lead to regression of some adenomas.[20] More recently, this disease has been proposed as an indication for hepatic transplantation,[24] which corrects the major metabolic abnormality in the liver, since the phenotype of the transplanted liver permanently retains its original donor specificity and removes any adenomas that may be present.

Liver adenomatosis may be defined as the presence of numerous (arbitarily >10) liver adenomas in an otherwise normal hepatic parenchyma, in patients without a history of glycogen storage disease or androgenic steroid therapy, which is also known to induce multiple adenomas.[17] In a recent report of five such cases and a review of eight previously reported cases,[17] it was suggested that adenomatosis affects men and women equally and is seemingly unrelated to oral contraceptive therapy. The age at time of diagnosis ranged from 13 to 75 years, and the progression of the lesions appeared to be slow. Malignant transformation had not been reported, despite the fact that it is a well-recognized complication of multiple adenomas associated with glycogen storage disease and androgen therapy.[25–27]

We now report a case of apparently spontaneous transformation to hepatocellular carcinoma 5 years after the original diagnosis of adenomatosis. The possibility that the original tumors were well-differentiated hepatocellular carcinomas cannot be excluded, but, upon reviewing the histology and in view of the length of evolution, seems unlikely. This patient has undergone successful liver transplantation, and there were areas of recognizable adenoma present in the resected liver among the hepatocellular carcinoma. In view of this malignant potential, adenomatosis may now be considered as an indication for liver transplantation.

Solitary or Two Adenomas

These tumors occur predominantly in women, and have increased in frequency over the past 20 years. Since the original report by Baum et al. in 1973,[28] a strong association has been demonstrated between liver cell adenomas and the use of hormone therapies, particularly oral contraceptives. Perhaps the most compelling evidence is the reduction in size of adenomas seen in some patients upon cessation of oral contraception.[1,2,12,20,29,30–33] Tumor involution after discontinuing usage of oral contraceptives is inconsistent and does not eliminate the risks of the tumor. These risks include hemorrhage,[1,9,34] which is often sudden and unpredictable, malignant transformation,* which is probably rare but unpredictable, and increase in size of the tumor,[37] which may eventually make its surgical excision more difficult or impossible. Two of our patients were initially observed after discontinuing use of oral contraceptives; in neither did the tumor regress, and in one patient, it actually increased in size. One other patient presented with an acute bleed into an adenoma 9 days after discontinuing use of oral contraceptives.

Our results confirm the serious potential complications of these tumors. Fifty per cent of patients presented with

* References 1, 4, 9, 13, 29, 31, 35, 36.

acute hemorrhage into an adenoma said to be associated with a mortality of 6%.[1] These bleeds occur in previously asymptomatic patients and are usually spontaneous, although occasionally a history of trauma is present. Similar incidences of this complication have been reported by others.[1,4,5,9] The frequency of hemorrhage into liver adenomas can be explained by their anatomical and pathological characteristics; adenomas are hypervascular tumors containing multiple sinusoids of dilated capillaries with thin walls and in which the pressure is high because the source of blood is exclusively arterial. The connective tissue support is poor, and a bleed therefore has a tendancy to spread diffusely throughout the entire tumor. Whether the hemorrhage remains confined to the tumor or produces hemoperitoneum depends principally on the distance separating the tumor from the liver surface and, if present, the thickness of the capsule, which, in our experience, has not been thick enough to be seen on ultrasonography or CT.

Most bleeds occur in tumors greater than 10 cm in diameter, but in this series bleeds occurred into tumors of only 5 and 8 cm. Bleeding into small tumors has been reported by others.[17,28] The diameter of a tumor after an acute bleed is, in any case, probably an overestimate of the true diameter because the hemorrhage often bursts the tumor.

We advise against the conservative approach to adenomas proposed by certain authors,[7,9,11-13] which involves the withdrawal of any etiological stimulus and observation. We recommend surgical excision of these lesions when this can be done without mortality or serious morbidity. Excision usually cures the patients of their symptoms, eliminates the possible complications of hemorrhage and malignant transformation, and eliminates the possibility of observing a malignant lesion that has been incorrectly diagnosed as benign. Several factors in this study appear to justify this policy: the high incidence of resectability, the absence of mortality or significant morbidity associated with resection, and the excellent prognosis on follow-up.

With its minimal operative risk, this series compares favorably with other reports where mortality following resection averages 9%.[2,3,5,6,28,38-41] A detailed study reveals that the mortality and morbidity reported were principally due to peroperative hemorrhage[3,6,41] or major hepatic resections, particularly of the right liver.[2,8,28,38]

Several features of the adenomas in our series explain the high risk of hemorrhage during resection and the occasional need to perform extensive anatomically-based resections similar to those performed in most of the published series.[2,5,6,8,28,39] First, adenomas were of maximum diameter >10 cm in 60% of the cases. Second, in the majority of cases, the topography was principally central or with central extensions. Third, the tumor-free liver parenchyma was often small, and in one patient, this rendered tumor resection unwise. The impossibility of excision of certain adenomas or the need to perform extensive resections incompatible with normal liver function in the postoperative period has been reported in several other series.[4,5,28,38] Fourth, the adenomas were hypervascular always with multiple arterial pedicles, and compressed the right or left portal branches and/or trunk of one of the three principle hepatic veins in 72% of the patients. The displacement of hepatic veins by the tumor also results in a compromise of the safety of the usual anatomical planes of the major liver scissurae, along which anatomical resections are performed.[18]

The success and safety of the resections we have performed can be reasonably explained by certain guiding principles. First, systematic arterio-portal control should be obtained to the area of liver being resected. When the risk of injury to a major hepatic vein is high, total vascular exclusion of the liver may be required. Second, dissection of the tumor should remove the minimum of nontumoral liver parenchyma; (tumorectomy should be performed whenever possible, formal anatomic resections only when an anatomic necessity). Third, dissections should be guided by peroperative ultrasonography, permitting the precise location of the limits of the tumor and the position of the principle vascular structures in contact with the tumor.[16] An ultrasonic dissector is a useful adjunct because the nontumoral liver has a normal consistency and allows easy separation of the tumor from peritumoral vessels.

The excision of an adenoma may be reasonably delayed when operating for hemorrhage in the emergency situation. The operative risk is higher,[2,3,5,42] and control of hemorrhage should be the aim. Residual tumor can be excised electively after further morphologic studies. Excision may also be delayed for very large adenomas when an intervention appears to be high-risk. In these patients, arterial embolization enables preoperative reduction in tumor size and vascularity.

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